Dos and Don'ts in the Management of Cirrhosis: A View from the 21st Century

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Cirrhosis is a morbid, multisystem disease associated with frequent hospitalizations and high mortality rates. The number of affected people is rising in the United States, reflected in a 59% increase in patients with cirrhosis seeking medical care in the past decade [1]. Anticipating and preventing many of the complications of cirrhosis can be challenging. To aid gastroenterologists caring for this booming population, we propose the following "Dos and Don'ts" for management of cirrhosis in the inpatient and outpatient settings (Table 1).

ALL PATIENTS WITH ASCITES ADMITTED TO THE HOSPITAL SHOULD HAVE A DIAGNOSTIC PARACENTESIS, REGARDLESS OF COAGULOPATHY

Spontaneous bacterial peritonitis (SBP) is often asymptomatic and early treatment is associated with improved outcomes. Accordingly, patients with ascites who undergo a diagnostic paracentesis on admission have reduced in-hospital mortality. There is no evidence that patients with elevated International Normalized Ratios or thrombocytopenia benefit from periprocedural prophylactic blood product transfusions [2].

TREAT SBP AGGRESSIVELY IN THE HOSPITAL AND START SECONDARY PROPHYLAXIS ON DISCHARGE

Following a diagnosis of SBP, patients should promptly receive antibiotics (Fig. 1). SBP is associated with the development of hepatorenal syndrome, thus 25% albumin solution should be infused to maintain intravascular volume to protect the kidneys [3]. Diuretics should be held until the infection has resolved. Empiric antibiotic therapy fails in up to 25% of cases; a repeat diagnostic paracentesis should be considered if there is no clinical improvement after 48 h. Long-term antibiotic prophylaxis should be initiated on discharge. Of note, data from randomized trials of patients without SBP suggest benefit from quinolone-based primary prophylaxis, specifically those with Child-Turcotte Pugh (CTP) scores $\geq$9 and bilirubin $\geq$3 or impaired renal function (creatinine $\geq$1.2 or sodium $\leq$130 mmol/L) and an ascitic fluid total protein $<$1.5 g/dL [4].

ACT QUICKLY FOR SUSPECTED VARICEAL BLEEDING AND DONT FORGET SECONDARY PROPHYLAXIS TO PREVENT RECURRENT BLEEDING

Patients with cirrhosis and upper gastrointestinal hemorrhage should undergo upper endoscopy within 12 h of presentation (Fig. 2). Prior to endoscopy, all patients should receive vasoactive agents and antibiotics. As patients with cirrhosis and gastrointestinal bleeding are at high risk for bacterial infections (not limited to SBP), antibiotics should be provided even if patients do not have ascites [5].

Patients who had a variceal bleed are at high risk for recurrent bleeding. Secondary prophylaxis includes starting non-selective beta-blockers (NSBB) on discharge and scheduling follow-up endoscopy to eradicate varices. Increasing data show that NSBB also improves all-cause mortality [6]. Early Transjugular Intrahepatic Portosystemic Shunt placement should be considered in appropriate candidates (CTP B with endoscopically active bleeding despite medical therapy or CTP C with a score $<$14), even if they do not re-bleed after initial endoscopic therapy (Table 2) [4].

INCORPORATE HEALTH MAINTENANCE INTO EACH VISIT, EVEN IF IT IS OUTSIDE THE SCOPE OF "TYPICAL GASTROENTEROLOGY" CARE

Vaccination status including influenza and pneumococcal vaccines should be assessed at each visit. Vaccination against hepatitis A and B are recommended in cirrhosis, but only one in three patients with cirrhosis complete this vaccination series [7]. Gastroenterology clinics should have the capacity to provide on-site vaccination.

Cardiovascular disease is prevalent in patients with cirrhosis, but owing to concerns of hepatotoxicity many providers are

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hesitant to prescribe statins. Statins are safe in patients with compensated cirrhosis, and current guidelines do not even recommend assessing liver enzymes after initiating statins [7]. Furthermore, there is mounting evidence that statin use is associated with decreased risk of decompensation and mortality [8]. Gastroenterologists should educate patients and other medical providers that statins should be prescribed when indicated in patients with chronic liver disease.

Table 1 "Dos and Don'ts" In the hospital

	Do	Don't
Patient presents with ascites	Perform a diagnostic paracentesis on admission	Delay the procedure for coagulopathy or transfuse blood products prior to procedure
Spontaneous bacterial peritonitis	Start antibiotics quickly and give albumin on day 1 and day 3	Forget to prescribe long-term antibiotics for secondary prophylaxis
Suspected variceal bleeding	Perform endoscopy and start medical therapy (vasoactive agents and antibiotics) quickly	Forget secondary prophylaxis (NSBB and follow-up EGD(s))

EGD esophagogastrodudodenoscopy, *NSBB* non-selective beta blocker

PROACTIVELY DISCUSS SAFE PAIN MANAGEMENT IN CIRRHOSIS

Over the counter and prescription analgesic use is common in cirrhosis. Acetaminophen is safe in cirrhosis if doses are limited to 2000 mg daily and should be used for first-line pain control. Nonsteroidal anti-inflammatory drugs should be avoided in patients with ascites due to the risk of renal injury. Many patients with cirrhosis chronically use narcotics. Judicious narcotic use can be safe but may increase the risk of falls and hepatic encephalopathy (HE) [9]. Non-pharmacologic modalities for pain including physical therapy, counseling, and yoga or meditation should be considered.

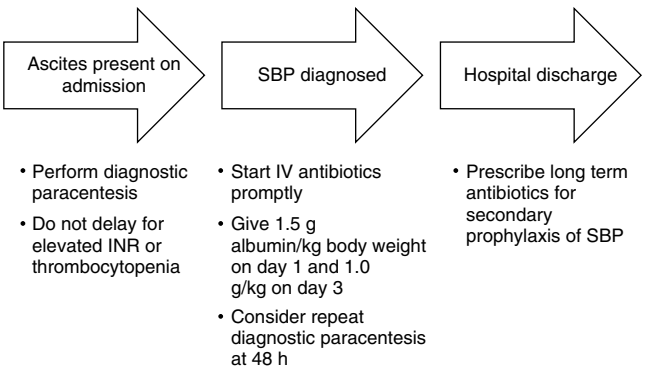

Fig. 1 Key points in diagnosis and management of spontaneous bacterial peritonitis (SBP). INR international normalized ratio, IV intravenous

REFER EARLY TO DIETICIANS AND DONT RESTRICT PROTEIN

The majority of patients with decompensated cirrhosis are in catabolic states and are malnourished, contributing to a host of adverse events including HE, falls, and disability [10]. Accordingly, protein intake should not be restricted. Cirrhosis patients should take in 1.2–1.5 g/kg/day of protein and 30–40 kcal/kg/day [11]. A nighttime snack should be recommended to help meet this goal. Providing specific dietary recommendations can be challenging given the need to balance sodium restriction for ascites (when present) and carbohydrate/calorie restriction for patients with non-alcoholic steatohepatitis or diabetes (Fig. 3). Thus, early referral to a dietician is helpful.

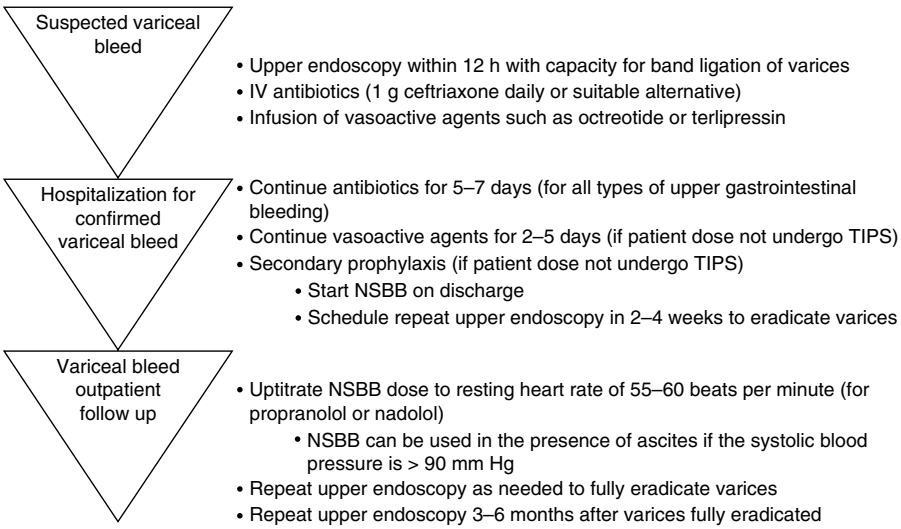

Fig. 2 Acute and Subacute management of Variceal Bleeding. IV intravenous, NSBB non-selective beta blocker, TIPS transjugular intrahepatic portosystemic shunt

Table 2 "Dos and Don'ts" in the clinic

	Do	Don't
Health maintenance	Assess vaccination status and general health maintenance issues (cardiovascular disease and smoking cessation)	Leave all health maintenance up to patients' primary care providers
Pain management	Discuss the safety of limited (2 g/day) acetaminophen use	Prescribe NSAIDs
Nutrition	Recognize malnutrition and refer to dieticians early	Restrict protein
Quality of life	Discuss common disabling symptoms in cirrhosis	Wait for patients to bring these issues up
Alcohol use	Screen for alcohol use disorders in all patients	Forget to reassess over time
Ascites management	Instruct patients on self-management, salt restriction, weight recording, and red flags	Wait until ascites becomes unbearable necessitating emergency room or hospital admissions
Hepatocellular carcinoma	Screen with ultrasound + serum AFP every 6 months	Leave patients out of screening
Liver transplant referral	Refer early when a patient develops decompensated cirrhosis	Wait until the patient is hospitalized in life-threatening condition
Palliative care	Address goals of care and refer to palliative care early	Wait until patient is in a critical state

AFP alpha fetoprotein, *NSAIDs* non-steroidal anti-inflammatory drugs

INQUIRE ABOUT AND MANAGE COMMON QUALITY OF LIFE SYMPTOMS IN CIRRHOSIS

Cirrhosis patients can experience debilitating complications that affect quality of life (Table 3). These include muscle cramps, pruritus, sleep disturbances, and sexual dysfunction that can improve with symptomatic treatment [12]. Patients may not disclose these concerns in a busy clinic visit, so they should be proactively assessed by providers.

SCREEN FOR ALCOHOL USE IN ALL PATIENTS WITH CIRRHOSIS, AND REFER FOR TREATMENT AS NEEDED

Continued alcohol use can worsen liver disease even when alcohol is not the primary cause of the liver disease. Patients often underreport how much they drink [13]. If there are concerns about recent use, alcohol screening tests can be used to detect alcohol consumption over the past week (e.g., urine ethyl glucuronide). Patients who screen positive for an alcohol use disorder should be referred for counseling and/or pharmacologic therapy. Alcohol use should also be reassessed during return visits, especially in the setting of worsening liver disease.

EDUCATE PATIENTS ON THEIR ROLE IN MANAGING THEIR ASCITES, INCLUDING EASY ACCESS TO OUTPATIENT PARACENTESIS IF NEEDED

Patients with ascites need to follow a two-gram sodium diet. This is challenging, so patients and their caregivers should meet with a dietician to learn how to follow this. Providers should instruct patients to record their current diuretic dose along with daily weights, and to call the clinic for large (≥5 pound) fluctuations in weight. Ensuring availability of and easy access to outpatient therapeutic paracentesis is essential as this has been shown to significantly decrease healthcare costs and 30-day readmission rates [14] (Fig. 4).

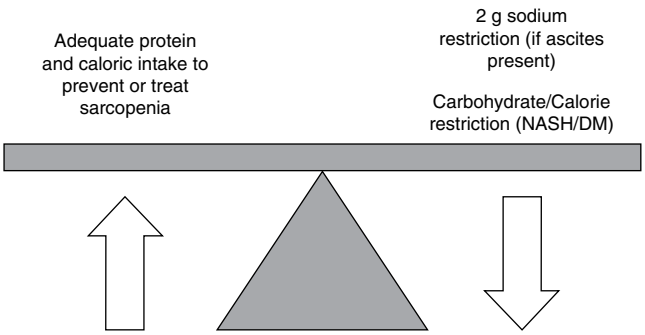

Fig. 3 Dietary balance in cirrhosis. NASH non-alcoholic steatohepatitis, DM diabetes mellitus

SCREEN PATIENTS WITH CIRRHOSIS FOR HEPATOCELLULAR CARCINOMA (HCC)

Patients with cirrhosis are at an increased risk for hepatocellular carcinoma (HCC), which has been rising in the United States. They should be screened for HCC with an ultrasound of the liver (±serum alpha fetoprotein testing) every 6 months. A recent systematic review of observational studies demonstrated that surveillance leads to earlier stage at diagnosis, higher rates of curative treatment, and improved survival [15]. To promote adherence, patients should be educated regarding the benefits of surveillance and automated orders/reminders for clinic staff should be programmed in electronic health records.

REFER PATIENTS FOR LIVER TRANSPLANT EVALUATION WHEN THEY DEVELOP DECOMPENSATED DISEASE

A patient's risk of death dramatically increases once they develop decompensation of their cirrhosis. Following such an event: variceal bleeding, ascites, or hepatic encephalopathy, referral for evaluation at a transplant center is indicated. While some patients

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Table 3 Screening questions and treatment options for common disabling symptoms in cirrhosis

Symptom	Sample Question(s)	Therapeutic options
Muscle cramps	• How often during the last 2 weeks have you had muscle cramps?	• Normalize electrolytes and fluid balance • Taurine (3 g daily) • Vitamin E (300 mg three times a day) • Baclofen (5–10 mg three times a day as needed)
Pruritus	• How much of the time have you been troubled by itching during the last 2 weeks?	• Moisturizing cream for dry skin • Cholestyramine (4 g daily) • Naltrexone (50 mg daily) • Sertraline (75–100 mg daily) • Ursodeoxycholic acid (13–15 mg/kg/day in 2 doses)
Sleep disturbance	• Have you had difficulty sleeping at night? • Have you felt sleepy during the day?	• Optimize treatment for HE • Optimize sleep hygiene • Referral to sleep specialist to assess for sleep apnea • Mindfulness training • Melatonin (3–5 mg daily)
Sexual dysfunction	• Have you had any sexual activity in the past few weeks? • How satisfied were you with your sexual function during the past few weeks?	• Phosphodiesterase inhibitors (e.g., sildenafil 25–100 mg as needed) • Sex therapy referral • Referral to Urology

HE hepatic encephalopathy

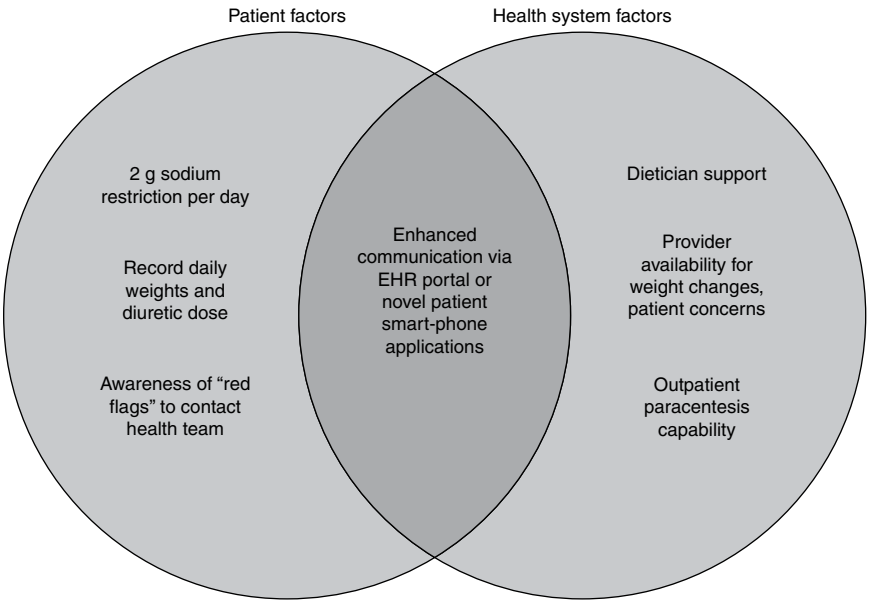

Fig. 4 Patients and health system factors associated with successful ascites management. EHR: Electronic Health Record

may remain stable for months after the first decompensation, the clinical course is unpredictable and further decline can be precipitous; thus early referral is important.

START ADDRESSING GOALS OF CARE IN NON-URGENT SETTINGS, AND HAVE A LOW THRESHOLD TO REFER PATIENTS FOR PALLIATIVE CARE

For all patients with decompensated cirrhosis, particularly when transplantation is not a part of their care, a focus on enhancing quality of life should be prioritized. Unfortunately, only 11% of patients with decompensated cirrhosis are referred for palliative care [16]. Patients with decompensated cirrhosis should be given the opportunity to address goals of care and establish a healthcare proxy. Earlier involvement of palliative care can help focus care on patient wishes, avoid futile interventions, and could reduce unnecessary procedures and hospitalizations.

CONFLICT OF INTEREST

Guarantor of the Article: Anna SF Lok.

Specific author contributions: Conception of the manuscript: MJT,

EBT, ASL Writing and revision of the manuscript: MJT, EBT, ASL
All authors approved the final draft that is submitted.

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